whether someone is going to get a benefit would be the position of the lead. As you pointed out in your presentation, you wanted a lateral free wall position and in the InSync data I believe you tracked where the lead actually was placed. There is data that if you have a position anterior in the great cardiac vein, 30 percent of patients will actually have decompensation in cardiac performance. Can you tell me the percentage that had a lateral wall position? Because I think it has a lot to do with operator experience and persistence whether they get to that position, and I think the acute data suggests that it has a bigger effect on the increment of improvement.

DR. LEON: I agree with your comments regarding what we feel may be optimal lead position and, therefore, the investigational plan recommended what we call a free wall position, away from the septum. If you look at the definition of the segments for lead position, we have them as posterolateral, lateral, and any one of those can meet the criteria of free wall pacing. If you add those two, they add up to 70 percent of left ventricular lead positions in the Class III/IV patients that were randomly assigned and implanted.

DR. WILKOFF: In addition, an analysis was done to look at whether there was a difference by location of the lead. You know, we have a bias that says that lateral or maybe posterior lateral positioning might be the best place to put these leads, but when the analysis was done there was no relationship between the effect and the position actually obtained.

Having said that, very few of these leads were placed anterior or apical. Over 80 percent of the leads were put in some position other than anterior, and those are the positions that I would presume would cause no difference. So, any other position, posterior, posterior lateral, lateral, over 80 percent of the leads were placed in those, what we think are prime situations.

DR. HAIGNEY: Thank you. I think I have taken up enough --

DR. LASKEY: Now is the time. I will exercise the prerogative of limiting everybody else's queries but I think the two primary reviewers should have the opportunity. So, do you have more?

DR. HAIGNEY: Thank you, Dr. Laskey. Regarding the lead implantation success and

survival, you had about a ten percent failure to implant and about ten percent lead dislodgement rate. I don't think that that is surprising for this new lead. I think you are asking a lot of this new technology, but I am going to be in favor of post-market study on this because I think that the attractiveness of the device is going to be affected significantly by how long we can expect the lead to continue to function.

My final comment is the device appears to be effective at converting VT and VF but in some of these devices, the people who are using off-label defibrillators with an LV lead, as you pointed out, there is a great deal of over-sensing that could lead to inappropriate shocks and I didn't see data on that in the packet. I understand that your technology is different and the fact that you are only sensing through the RV is a big improvement theoretically, but did that actually translate into a reduction in inappropriate shocks?

DR. WILKOFF: I would like to address that. First of all, I would like to say that functionally the way that this device detects arrhythmias, both ventricular arrhythmias and superventricular arrhythmias and tachyrhythmia

discrimination between the two is functionally identical to the GEM-2DR, which is virtually identical to the GEM-DR which was presented before the panel here. It senses off the right ventricular lead. All the intervals, all the algorithms are identical to that situation. In every dual chamber device there are trade-offs that have to be made between programming the pacemaker versus detection and tachycardias. Those trade-offs exist in this device, just like they exist in the GEM devices preceding them. So, they are functionally the same.

There is a difference though. The difference has to do with the philosophy in the way these devices are programmed, and the difference is that in the GEM series you try to encourage intrinsic conduction so you program the AV intervals long. That extra interval that you allow the program long actually interferes more with the being able to program the detection intervals down into the slow VT. While, in the biventricular pacing modes you actually try to shorten the AV intervals.

[Slide]

Here we have programmed sensed AV delays.

This comes from the GEM-DR, and you see that the mean programmed sense AV delay was 72 ms. shorter, which is 72 ms. available for programming either up the rate response or up the upper limit or down the VT detection rate. So, there is even more opportunity to get what we call interlocks out of the way, get rid of the inherent problems with dual chamber pacing combined in a defibrillator.

[Slide]

As it turns out, the detection intervals were programmed the same between the GEM-DR, where you see it is at 395 ms. versus the treatment control limb of the InSync ICD. So, functionally people did the same thing they would have done as if they had a non-biventricular pacing defibrillator. That was true both for the VT zone and the VF zone. So, not only could you possibly have more room to program it, doctors were doing exactly the same thing that they did with the other devices.

[Slide]

I would like to discuss an analysis that I have done and I published on the GEM-DR data, published in Circulation, where I approached the issue of looking at how we should analyze

sensitivity and specificity of VT and SVT discrimination. We did an analysis in the GEM-DR population, the 933 patients, and I did the same analysis on the InSync ICD patients, 371 patients.

What this looks at is both the sensitivity for detection of ventricular tachycardia and ventricular defibrillation and also the specificity, making sure that we appropriately detected superventricular tachycardia, and inherently there will be some inappropriate VT/VF episodes that you will treat. The bias is towards treating things that are SVT instead of missing VT/VF episodes. All of the VT episodes were detected. But if you look at the inappropriate VT/VF episodes, what you see is that the raw numbers were 11.6 percent in the GEM-DR and 14.2 percent in the InSync ICD patients.

What you have to also understand is that there needs to be an adjustment of these rates by the generalized estimating equation which corrects for multiple episodes in an individual patient. It is possible that one patient would have 100 episodes that were either detected or not, and that would dominate the data. So, you have to do this adjustment in order to say that these are

comparable. Once we do that, we see that the rates are 21.9 percent versus 21.3 percent.

Essentially, theory would say that because they are identical algorithms they should be the same, and in practice they were identical here.

One more important thing, one of the issues that needs to be considered is were there any new ways that the defibrillator could mess up, and the answer is there were no new mechanisms, no new ways that SVTs or VTs were maladaptively detected, meaning that the same types of issues with the algorithm that were seen in GEM-DR are still issues here, but they are patient-dependent and they are equal within the populations.

DR. HAIGNEY: So, you are saying there was no difference between having therapy turned on and turned off?

DR. WILKOFF: No difference between therapy on or off; no difference between this and predicate devices, things that have come before it; no difference in the programming of this device and, indeed, if there is a difference it is in the philosophy of how they are programmed, which allows you to program down the VT detection rates to pick up more slow VTs.

DR. EWING: I would just remind the panel again that this data has not been submitted to the FDA; not been reviewed.

DR. WILKOFF: That is right.

DR. HAIGNEY: My last issue, as I have said, the device appears to be effective at recognizing and converting VT/VF. The one area where it seems to be less effective with therapy turned on is in the treatment of fast VT with antitachycardia pacing when you are pacing from the CS and the right ventricle, where I believe I saw a significantly lower incidence of cardioversion, not in treatment of VT but of fast VT.

DR. WILKOFF: You are right, the raw numbers that were reported in the packet suggest that RV alone, ATP and the faster ATPs was 98 percent versus 71 percent. But I think the small numbers really are problematic. There were only 17 patients that had ATP in the fast VT zone with biventricular stimulation.

But there may be something more there. I just think it is interesting to look at that. I suspect it is something that could be looked at more closely later. On the other hand, in the VT zone it looked like it was flipped around. But

neither one of those analysis were randomized analyses and what it does, it generates a hypothesis that perhaps there is a variance which would be better. Maybe in one zone you would want BV and in one zone you might want RV, but we would have to do another study to answer that kind of question.

DR. HAIGNEY: Thank you.

DR. PACKER: Dr. Laskey, in the spirit of what Dr. Ewing just reminded us of, which is to try to emphasize data the FDA has seen as opposed to the analyses they haven't seen, I just want to address your question about subgroups. There have been a lot of analyses on subgroups, including QRS duration, as a continuous variable, as a determinant of response not in this trial but in InSync, the original study which was done in patients without an ICD indication. As you can see, the results in the two trials are very parallel to each other. So, we feel a lot more confident perhaps in answering your question about subgroups based on the database which already has been fully interrogated, validated and submitted to the FDA. In that database QRS duration, looked at as a continuous variable, was not a determinant of

the efficacy of resynchronization therapy.

DR. LASKEY: You say it was not?

DR. PACKER: Was not.

DR. LASKEY: Mark, do you have any more questions?

DR. HAIGNEY: No, thanks.

DR. LASKEY: Again, I would like to keep us on schedule so if we could limit our queries to 20 minutes, if that would be feasible. Dr. Wittes?

DR. WITTES: First, let me assure you I am not going to ask for any analyses on the spot. I would never have the guts to do it and I won't ask for it.

I have three classes of questions. I don't think I am going to take 20 minutes. One has to do with whether the efficacy that we are seeing is a mirage, and I will come back to why I am asking that. Second, if it is not a mirage, how do we interpret the trivariate endpoint? The third issue is the problem of assessing interference. So, let me take them one at a time.

The question about the mirage actually has to do with the administrative censoring. We are looking at 224 patients randomized. I assume, but let me ask if this is right, these are the first

224. So, my question is why are we doing this. Why not wait until all? And, had you not found significant results in at least one of these endpoints what would you have done?

DR. ABRAHAM: I will address that question. I think the analysis that was performed in the cohort was prespecified. It is important to note that these were patients who were consecutively enrolled or randomized in the trial, and that the prespecified sample size calculation based on the endpoint which required the largest sample size, which was quality of life, indicated a need for 112 patients in each arm of the study, control and treatment, or a total of 224 patients. But as many of us who have been used to operating in the drug arena have learned in the device arena, trials like this often will continue enrollment beyond that. But the administrative censoring is that these are patients who had not yet completed six months follow-up at the time that this database was locked and prepared for the PMA supplement or the presentation to this committee. But that cohort of patients fully meets the predefined needs of the study.

DR. PACKER: If I could address that,

Jean, when I was this I thought it was very weird because the conventional practice would be that you do a study and you finish it; you look at the data and you present it. I know that sounds old-fashioned but that would be the sort of way that one would normally do this.

But I understand that what happened here was that there was a predetermined number of patients that, according to the original protocol, would be required to have enough power to test all three co-primary endpoints, with the largest sample size being driven by quality of life. And, that the sponsor made a determination, I think after discussions with the agency, that they would get all the patients up to the amount of patients that would be dictated by the trial. That is, they would not over-subscribe the trial. They would recruit as many patients as necessary to test the three primary hypotheses. They would essentially lock the database and that the fate of the trial would be determined then and there. I specifically asked the statisticians from Medtronic yesterday just suppose this trial had not met its primary objective at 224, would you have been tempted to have allowed the trial to continue and include the

patients who were recruited afterwards? And, they said that would be a violation of the way we thought about this process. We were locked into the 224. All the patients after 224 are simply patients whom we will continue to follow for safety and, regardless of what the results are in those additional patients, they would not accept the conclusion. Basically, the company made the decision that the protocol said 224; they were locked into 224; they would live or die basically on 224.

DR. WITTES: Thanks. Let me ask you this, is that written down? Do you have the words of that written in the protocol? Do you have a slide of that? Obviously you know where I am coming from. Suppose you had had instead of 0.0167, you had had 0.0169 would you really not have looked at the rest of the data? It is hard for me to believe that. Now, if I see it written as this is what we are doing. This study is 224 and all the rest is commentary, that would make me feel better. If it is a retrospective statement of intent, I have a hard time.

DR. PACKER: It is my sense, and we will endeavor to find specifically what you are asking,

that this was an a priori agreement with the agency to do exactly what was said. We will try to find it exactly, but I think we are all very sensitive to the specific concern that you are raising and it is my understanding that this was done entirely-- that the sponsor determined a priori that they would live and die based on 224. But we will continue to look for what you are looking for.

DR. WITTES: Good, I want to see the words. Next, I will just make a statement, it is not really a question. I would have preferred to have seen the Class IIs. It seems to me that even though this is for a Class III/IV indication they would have informed the way we look at the data.

DR. ABRAHAM: I will just add that I am certain that you will eventually see the Class IIs. You know, Class II patients were included in this study really for exploratory reasons. This was our first attempt, in going from the InSync trial to the InSync ICD trial, to begin to look at a group of patients that might be judged to be less severe, at least according to New York Heart Association class. As you know, there is a different prespecified endpoint for the Class II population, and that is peak VO2. In fact, much of that data

is still not in yet because of the core laboratory's ability to interpret those tests, but that data will follow. Again, the focus of this presentation, as described prospectively all along from day one and clearly identified in the study protocol, was this initial focus for the pivotal or key part of the trial in the Class III/IV population.

DR. WITTES: I understand that the efficacy endpoint for Class II is different from Class III/IV, but just as you are using the InSync data to augment and to explain and to give us comfort that what we are seeing in this cohort is something similar and coherent and consistent with what the previous data are, I think so would some of the information from the Class II, the lead information, the interference information and so forth. So, that is just a comment.

DR. PACKER: My understanding is that the FDA actually provided specific guidance to the sponsor to restrict their presentation to Class III/IV. I agree with you that one always learns more by looking at all of the data rather than less of the data, and that looking at internal consistency across all available data, InSync

versus InSync ICD, II, III, IV would always be useful. But that is not the guidance that was provided to the sponsor for this meeting but, you know, one can't ever argue against looking at more data rather than less data.

I was also just informed by the sponsor that it is their understanding that there are minutes, which they do not have with them but which will document the agreement with the Division to live or die based on 224.

DR. WITTES: Thank you. Can we get now to the interpretation of the efficacy endpoint? I have two very different questions here. One is how do you interpret the three endpoints. Let's do the second one first because I think it is easier, what does a 10-point difference on this scale mean? Milt, you already told us that this kind of difference is what you see in other heart failure trials. Those of you who know me, know I usually ask for aggregation of things, what I am not asking for is this aggregation because we have a scale that measures lots of different pieces, and the question that I am asking is, is there a part of the scale that changed? So, that is a disaggregation question. Secondly, what does ten

points mean? Those are not unrelated.

DR. PACKER: Well, the quality of life instrument, those who developed the instrument have gone back and identified components within the instrument which they have labeled a physical domain and an emotional domain. If they were here, they would say that that was not part of the original design of the instrument but has been a useful way of taking the various questions that comprise the instrument and putting them into categories that might be informative.

Occasionally one sees sponsors who don't achieve an effect on quality of life in its totality, who argue that their intervention has improved quality of life because they would then do a subgroup analysis and show that the effect was primarily in "the physical domain" which one might think would be the domain that might be best influenced by heart failure.

But here the effect was seen in the overall instrument. If one breaks down the effect, there are directionally favorable effects on both the physical domain and the emotional domain here. I venture not to do this, but if you look only at the physical domain here, it is actually even more

strikingly significant. But the effect in the emotional domain is still there and is directionally concordant with the effect on the physical domain.

DR. WITTES: Thank you. Now can you tell me what ten points mean? Can you calibrate it to something?

DR. PACKER: I think if you ask Tom Rechter and Jay Cohen who were instrumental in developing this scale, they would say, and I am trying to summarize what they would say, in their validation experiments they determined that anything that was different than five was "clinically meaningful." I don't know how they determined that. I am just citing what they have said at various forums to talk about the benefits of their instrument. I think that one needs to not only look at quality of life in terms of the magnitude of the effect; one has to look at the magnitude of the effect on other endpoints.

Setting aside for a moment what is primary and what is secondary, whether nominal p's were achieved or not achieved, one needs to look at the totality of the benefit seen across all measures of efficacy in this study. You have ten points in

quality of life which is, again, comparable or exceeds what we see with drug therapy. We have a one full New York Heart Association class in terms of New York Heart Association functional class, which is very meaningful. We have a 90-second difference in exercise time, which exceeds dramatically anything we normally achieve with drugs. We have nearly one ml/kg/minute increase in peak VO2, and we have this clinical composite which looks really very, very good and measures the totality of response retaining all patients in the analysis. So, we can more easily answer your question by not only focusing on quality of life but looking at the totality and magnitude of the treatment across all endpoints. If we do that, then what we are seeing here is clinically very meaningful.

DR. WITTES: That then, of course, segues directly into this trivariate endpoint because I think one of the problems I am struggling with here is that you have nominal significance for the measure that is the hardest to interpret, at least for me, the quality of life scale. You have almost significance for the New York Heart Association class but we have already heard that 49 of those

cases were unblinded. So, although we can grab at that because it is a one-step scale and I know there is a big difference, to me, that clouds the issue. Then, nothing on walk time.

What the conclusion says is that improves the quality of life, functional capacity and exercise tolerance. So, I need to throw back at you how are you interpreting Hochberg? My understanding is you are basing the inference on the Hochberg. Let me just say for those of you who don't play with statistics a lot, multiple comparisons is one of the hardest things that we deal with statistically, and there are Talmudic discussions about how to make inferences out of Hochberg. So, I think this is actually pretty important here because it reflects the way you are going to translate the words.

DR. PACKER: Well, I don't even know who Hochberg was.

DR. WITTES: He is alive; he is quite alive.

DR. PACKER: Oh. But I think the conclusions are based on both primary and secondary endpoints. So, the exercise that is incorporated into the summary of conclusions refers to the

secondary endpoints of peak VO2 and exercise time, and not the primary endpoint of the six-minute walk test. My understanding is that the Hochberg procedure is a mechanism of preventing reaching a conclusion when one is not warranted, and preserving the experiment-wise alpha of 0.05. My understanding is that was achieved here so that one, in fact, can conclude that the study did meet its primary objective. Am I missing something?

DR. WITTES: Well, let me tell you what the issue is and I won't be coy, I will tell you how I think too. The issue is that the way this works, this Hochberg game, is you make a hypothesis, and this is a three endpoint hypothesis. Then, if you get statistical significance by this rule, the question is what are you allowed to say? There are some statisticians who will say you are allowed to say that among these three things something was significant. Well, to me, that is not a very helpful conclusion. It seems to me that the conclusion is, oh, I got statistical significance on the quality of life and that is how I would interpret it. But I want to know how you, guys, are interpreting it.

DR. YOUNG: Let me make a comment about

this too because in choosing endpoints for clinical trials like this, non-morbidity, mortality trials, we do struggle with these "meaningful" endpoints and the ones that were utilized in both InSync and InSync ICD do match up with clinically meaningful endpoints that are frequently seen in clinical heart failure trials.

We did have discussions about whether or not to include as one of the third points MVO2 as the third measure and we weighed, as we often do, the pros and cons of having MVO2 up front and six-minute walk on the back side. Of course, in this particular trial, both trials, if we would have picked the maximal exercise test then we would have won perhaps on both things.

DR. WITTES: That is betting after the horse has run.

DR. YOUNG: I have no problem with that and that is not what was done. I can go back and explain why that wasn't done but it comes back around to my view of this, as a non-statistician but as a clinician looking at these things, we have three meaningful endpoints that perhaps are not as directly linked as we would like all the time, and you can see disparity of six-minute walk and

quality of life in both directions but each one of them still has meaning with respect to heart failure clinical trials.

So, I think there are three very important endpoints, and I think that because we don't know that they are directly and intimately linked--because you wouldn't have to use the Hochberg if we knew that they were absolutely intimately linked and if you got (a) you would get (b) and (c)--it is an appropriate choice for a clinical trial design like this.

DR. PACKER: Maybe I can just address this.

DR. LASKEY: We are going to need to get off this Talmudic discussion and proceed so unless it pertains to something other than Hochberg and the corrections, because I would like to move this along.

DR. PACKER: I will be very fast, just to clarify the situation, New York Heart Association class did, in fact, make the Hochberg criteria according to the sponsor's prespecified analysis, which I do not agree with, but it did make it according to the way we would normally analyze data in a heart failure trial, which is intention-to-

treat with less value carried forward, not baseline, with post-randomization double-blind value carried forward. The way that these data were presented today is a completers analysis. I get nervous about completers analyses. So, if you do a last observation carried forward on post-randomization data, the New York Heart Association class actually makes it using the Hochberg criteria.

DR. WITTES: Let me address interference very briefly. I had a very hard time, as I was reading the panel pack, figuring out how to get at this question. The only question I will ask because I am sure other people are going to ask this later is in the VT detection time there is the difference between 3.8 seconds and 3.4 seconds, which is not statistically significant but my question is two-fold. One, is that large? I don't know whether that is a big difference or not. Two, what are the Ns? Are they patients or episodes?

DR. WILKOFF: Those are very small differences. It depends on the cycle for the tachycardia. There is a certain number of intervals needed to be detected. So, if the tachycardia goes a little bit faster, it will go

minimally shorter; if it goes a little bit smaller, it will go minimally longer. But 3.4 to 3.8 seconds is not clinically significant and, indeed, you have an option for prolonging the number of intervals to detect from 12 to 18. If you look at that analysis, when you went over a longer period of time it actually was faster with the device on. Since it is identical to previous devices, there is no reason to think it should be any different. There is no reason to think it should be any different in either case, and it is not a clinically significant difference.

DR. WITTES: And the Ns, what are they? Patients or episodes?

DR. WILKOFF: Those are episodes.

DR. WITTES: Was the analysis done taking that into account?

DR. WILKOFF: You mean multiple episodes? What do you mean?

DR. WITTES: Was it done adjusting for the clustering?

DR. WILKOFF: That particular analysis was not done in that way, no.

DR. WITTES: Then I wouldn't pay any attention to the p value.

DR. WILKOFF: Okay.

DR. YOUNG: Can I come back to one issue that you mentioned a minute ago about 46 episodes of unblinded assessment of New York Heart Association classification? That in fact wasn't really the case. If you looked at the unblinding that occurred, there were only four episodes where the heart failure physician who was responsible for the blinded New York Heart Association assessment knew whether the CRT was on or off. The unblinding issues were a lot of other more technically related issues on who was performing exercise testing, etc., etc. It wasn't related to the New York Heart Association except in those four patients.

DR. WITTES: Thank you. That is very helpful.

DR. LASKEY: Dr. Domanski?

DR. DOMANSKI: I think I can be reasonably brief but I do have a few questions. One of them is very specific and maybe just a yes or no answer. Did you look at the relationship between QRS shortening and outcome? I mean, can you predict outcome from QRS shortening? If people shortened their QRS more, did they do better? Because that hasn't been a finding elsewhere and I am just

curious about what you found.

DR. ABRAHAM: That analysis has not been performed for the InSync ICD study; it has for the InSync, and there was no relationship between the degree of shortening and primary endpoints.

DR. DOMANSKI: Which I guess coincides with the literature. I want to back off briefly and look at the big picture of this, and it seems to me that the resynchronization therapy is enjoying a close look around the country and around the world. We don't, to my knowledge anyway, know that it reduces mortality to resynchronization the ventricle, but the data that you present are more or less in line with other data that have been presented that have nothing to do with this submission. It doesn't seem to me that the data that they are coming in with is markedly at variance with what is out there.

But I think two things. So, what this device seems, to me, to be doing is to present the capacity to resynchronize patients who need a defibrillator without needing a second device, and with a device that has fairly integrated function. So, if this is to fail in effect, because you presented data on safety and effectiveness, but if

they are to be impugned, they have to be impugned, it seems to me, on one of two bases. One is that the device just doesn't work; it doesn't do what they say it will do. And, you know, I can't even come up with a question that asks that because it looks like it does more or less what it says it will do.

The second way that it could fail, it seems to me, is if the clinical trial itself was flawed. There are only a couple of ways that one could see it failing. One is because of just bad design. The business of 224 and stopping at a particular thing strikes me that you don't have a super hard endpoint here, and in the absence of a very hard endpoint one needs to look carefully at process. It seems to me though that the FDA must have something in their minutes, or whatever, that you promised to stop at 224. Now, knowing the people that are there, if you say that you said you were going to I actually believe you, but in the public interest to take people with an obvious vested financial interest in the thing and accept that is probably not acceptable. So, I would ask the FDA to either come up with something that is a matter of their record or, secondly, find it in the

protocol somewhere.

I think that is important, and if you can't do that then I think that what would have to be done is not just rejecting the thing but there ought to be an analysis that is provided to the FDA before the thing is approved that looks at both the 224 that you are presenting here today and what happens if you look at the whole thing. If they are concordant, then, you know, no harm, no foul I guess. But if they are not, I guess that approval of this thing--I am not sure that it would rest on adequate grounds and I can't ask you a question that answers that right now. It seems to me to be a straightforward point. If it is prespecified, and I am saying this to the FDA now, I wouldn't look at that as some kind of a smoking gun.

The second thing is that I guess one can pick away at exactly how many patients got unblinded. I can't see a smoking gun there either. You know, you don't want folks unblinded when they are supposed to be assessing New York Heart Association functional class but it looks like the numbers were small and, unless somebody is smarter than I am, I don't care to pick here for the next ten minutes at each one of those patients because

it is not entirely obvious to me.

The third thing goes to labeling, and here I would be interested in some comment maybe from Dr. Packer first. There is no question that when one looks at the whole field of defibrillation one seeks to define who, inside a clinical trial, actually benefitted, that is, look at subgroups as one of the primary reviewers did. I am concerned about that in this FDA process because it is hypothesis generating but when you have in front of you a randomized trial you have a population that you know either did benefit or didn't benefit, and we don't really don't know who did inside. But even if your subgroup analysis suggested strongly one group, I think it is inappropriate to use the retrospective analysis inside one trial to try to define indications. So, I would counsel advocating that, that kind of discussion relative to indications, and I would be interested in some comment from maybe Dr. Packer and their statistician and how they feel about that as a basis for indications because that could be an issue later.

DR. PACKER: Gee, Mike, this could take an hour.

DR. DOMANSKI: No, don't, please. I want to take about two minutes.

DR. PACKER: Let me just say that the conventional regulatory practice is to label a device based on the definition of the patients who were enrolled in the trial overall, and to look at subgroup analyses as a mechanism of defining consistency of a drug or a device effect, and not to overemphasize them because they can be problematic. I think that is a guidance which has almost invariably been followed, although I can think of one recent exception but not on the device side. So, I think your statement is correct.

DR. ABRAHAM: I just want to briefly comment on this N of 244. Jim and I were lamenting the fact that we never authored a design paper for the InSync ICD trial but we did, in fact, author one, and it is published, for the InSync trial and it clearly describe, if you remember the language, the pivotal phase and it clearly identifies the N of 244 as being that cohort. I know that requires some leap of faith. I expect we can find the documentation from discussions specific to InSync ICD but again, remember, the trials were developed to be identical in that regard.

DR. PACKER: Let me just say that I think this is an extremely important point because it is really easy for sponsors to gain this, and that is what Janet is worried about. But Mike's solution here is the appropriate solution. Either there is documentation or there is not. If there isn't, then my sense is that a recommendation for approval would be contingent on making sure that the totality of the data is consistent with the effects that you have seen today.

DR. ZUCKERMAN: I would like to give a partial agency response to Dr. Domanski's question, which is an important one. I think the FDA, I believe the lead reviewer Doris Terry, showed a slide this morning where initially the sponsor came in with a partial data set and there was a desire to somehow pool that data with the original InSync. Then we have these data that were presented this morning, and perhaps Dr. Gray or Dr. Barold can give our position that we gave to the sponsor.

DR. GRAY: Regarding the pooling?

DR. ZUCKERMAN: Not regarding the pooling; regarding the actual number that we were interested in seeing. Dr. Gray, who is our biostatistician, is coming to the podium.

DR. GRAY: That is a tough question. As far as I can recall from the design phase of this, the sample size was specified as 224. So, that was the prespecified sample size. I don't recall a promise of stopping if there was failure at that point. I can't answer for sure without looking at the minutes of the meetings to know that. First of all, I know there was agreement that the minimal sample was 224 but I don't recall that there was also, combined with that, an agreement that we were definitely going to stop at 224 and not continue. So, without seeing the minutes from the meeting I can't definitely say that there was a promise to stop.

DR. DOMANSKI: Well, maybe in the rest of the session we can do that as some kind of a condition or something. It is an important point. I don't care what was in their heart as long as it was written --

[Laughter]

I guess it would be nice to know it was written, or the analysis ought to be done and I think that ought to become a condition of approval. Have you analyzed the other data? I mean, have you actually run the numbers? I don't want the result,

for obvious reasons. You haven't run it? You have no idea what that would show? Okay, well, that is interesting. That is all I have.

DR. LASKEY: Dr. Konstam?

DR. KONSTAM: I am fairly concerned about the interpretation of the primary endpoints and their meaning. Let me just comment about the magnitude of the effect. I agree with everything that has been said. When I think about magnitude of effect, I think it is important for a few different reasons. One is do you believe it? Two is, is it clinically relevant? Three is, is it clinically relevant relative to the intervention that was required to get there?

Just to touch on the last one first, I certainly can accept, if we believe the result, that it is of a magnitude that probably has clinical relevance. There may be some patients who have substantial benefit; there may be some patients who have no benefit. So, if we believe the result I don't have any problem accepting that it is likely to have clinical relevance.

I think one must ask though is it worth the intervention that was done in terms of the fact that this was an interventional procedure, in terms

of the morbidity of the procedure, and maybe we have to come back to that.

With regard to the first question, I am still sort of stuck there. Is the result real? I guess there, if it were an enormous magnitude it would help. The fact that it is, to me, a modest magnitude sits there.

Then I come back to the other concerns I have. I am not concerned about this 224 business. I find it very annoying because it ought to be in the protocol. If it was the intent to stop the study at 224 patients, it ought to be in the protocol. If it is not in the protocol, then I just cannot accept that was the solitary intent and that there would not have been some continued looking had the result not hit it. So, I think we need to see it in the protocol.

The other things that raise question about whether the primary endpoint is real or not relate to the number of endpoints there. There has already been some discussion about that. I actually want to ask about the Class II analysis because it strikes me that there is a fourth primary endpoint in the overall study, namely, VO2 max, which was the primary endpoint prespecified

for the Class II patients. So, I guess I want to just mention that that is sort of another primary endpoint sitting in the trial and ask any of the statistical people in the room whether they want to comment on should there be a penalty for that. There is another endpoint within the trial. I know what you would say, Milton. How about some of the statisticians?

DR. WITTES: It wouldn't bother me at all. I see it as two different trials.

DR. KONSTAM: You see it as two different trials?

DR. WITTES: Yes. So, I wouldn't correct for that.

DR. KONSTAM: And it is clear from the protocol that it is two different trials?

DR. WITTES: I don't know, I haven't seen the protocol.

DR. KONSTAM: So how do you know it is two different trials?

DR. PACKER: I think that here the protocol specifically says that the primary endpoint--I think Janet is right, it is as if this were two different trials. The protocol makes it explicitly clear.

DR. KONSTAM: That is fine. I don't want to get hung up on that. So, we are left with three primary endpoints. I guess the thing that is most concerning about the interpretation of the primary endpoint is this question of unblinding. So, the one component that is most clear, I guess, is the one that is relatively subjective. The most objective one doesn't even really trend in the right direction--well, maybe it trends a little bit; no, it really doesn't do much of anything. I want some more clarification about this unblinding thing because I am concerned that we are sort of seeing the tip of the iceberg in terms of unblinding. I wonder whether we could ask Dr. Barold to expand on this? Was it 69 protocol violations? What was the number, 67, 69?

DR. BAROLD: Right. The way we obtained that number was that I think in one of the last appendices of the huge volumes that the sponsor gave us there is a line listing of protocol deviations. When we looked at the crossover rates, the fact that they were sort of unilateral crossovers for congestive heart failure, I decided to take a look. We don't typically go through each line listing in the protocol for deviations but I

went through them and just counted how many were associated with blinding. These basically come from the case report forms. There is very limited information. It is one line. Some of them were pretty obviously not a big blinding issue so I discounted them. For example, something that would be listed as a blinding issue would be somebody that was not supposed to be blinded looked at the list. I didn't consider that a blinding issue. But I have very limited information on what these exact blinding issues were, and these were just things that were reported to the sponsor that then were reported to us. So, we don't have a full view of what the blinding issues were. We just have what the exact protocol deviations were.

DR. KONSTAM: Again, I think this is important because, number one, in this study there is a lot of opportunity for unblinding and, two, the endpoints are very subjective. So, I think this is really a critical issue.

I just want to ask the investigator sitting at the table what their comment is about these ten crossover patients. As I understand the situation, there were ten crossovers from on to off because of--

DR. YOUNG: From off to on.

DR. KONSTAM: Sorry, from off to on. You are right. From off to on because of worsening heart failure. None in the other direction. So, obviously, if you are going to go from off to on you have to know that you are off and that occurred exclusively in the off group. Doesn't that mean that there was a substantial unblinding problem going on?

DR. YOUNG: Let me specifically come down to the blinding issues and talk about it in totality because this is extremely important. We are used to the placebo-controlled clinical trials of a medication which, albeit flawed, are much easier to achieve blinding in than in an intervention sort of thing. Up front this was a huge concern. So, both in InSync and InSync ICD an awful lot of things were done at the very beginning to try to create a double-blinded clinical trial.

To go back to the beginning, when we started with our investigator selections, as well as with the education of all of the sites, we, in a little bit of an unusual fashion, matched heart failure clinicians with electrophysiologists. The fact that we are all sitting at the table up here

shows that there is a new paradigm out here. The concept was to, up front, deal with this issue by keeping the heart failure clinicians or the cardiologists responsible for the heart failure care blinded during the management of these patients to the electrocardiogram and whether things were on or off.

The other thing that we did was that the quality of life was patient administered quality of life. Whether you like it or not, or think it is strong or weak, it is a patient self-administered sort of quality of life tool.

Then, in terms of some of the secondary efficacy endpoints, like the MVO2 and the echo endpoints, we had separate laboratories designated who were not involved at all in the trial and had no communications with any of the investigators.

What we also did, we went to great lengths to have the unblinded clinicians, the electrophysiology group who had to handle programming issues and those sorts of things, in fact, be unblinded.

Finally, the counts that Dr. Barold was alluding to were counts for IIs, IIIs and IVs. If you look at the count for III and IV patients,

there were 37 patients with 57 protocol deviations and in that group over 80 percent of those protocol deviations were somebody performing the six-minute walk or the metabolic exercise test or the echocardiogram who wasn't on the list saying that this person was blinded to the patient being on or off.

The real issue is how many of the patients had the heart failure staff who were supervising that end of the care and that end of the analysis unblinded, and there were four patients, 11 percent, that were unblinded to the heart failure staff.

Interestingly enough, if you go to the patients who were off, had worse heart failure and went on, those ten patients, I can tell you a lot about that because the mechanism for allowing the movement had to go through a series of phone calls and, as one of the PIs, I ended up being the person who would get all the phone calls from the people who were out in the field. Nine of those phone calls came from these guys, the electrophysiologists, the ones who knew the patient was unblinded and during the follow-up period. Because of the worsening heart failure and the

worsening condition of the patient, they knew the patient was off and they began the process of switching the patient to an on patient.

DR. KONSTAM: Well, that doesn't make me feel more comfortable because that suggests that the EP people who were unblinded were participating in the clinical management of the patients. Let me just say I don't for a minute question your intent to do the best you could in this situation where there is so much potential for unblinding. So, I don't challenge that for a minute. I just think we are left with a couple of primary endpoints that are subjective. The fact that the quality of life form was filled out by the patient doesn't help me too much because if the investigators are unblinded, then I think the patient is likely to be unblinded too. Or, you certainly can't say that he or she isn't.

One way or another, if there is a unidirectional movement from off to on because of worsening heart failure, I conclude that there is admixture of the clinical evaluation and the knowledge of the treatment going on, whether it is the EP people talking to the heart failure people or the heart failure people are seeing the EKGs.

The other thing is my inference, right or wrong, is that we are seeing the tip of the iceberg. If we identify these line items in the case report forms, if we have these ten patients, to me all bets are off. In my mind, despite your best efforts, there may be some substantial amount of unblinding going on.

DR. BAROLD: The agency just wants to clarify some of the line listing. I know you brought up four patients that did this or that. We haven't actually discussed how we coded things with the sponsor. So, we were very conservative in that we gave the sponsor as much leeway as possible. We haven't reviewed how you dealt with the blinding issues as compared to how we dealt with the blinding issues and the four patients that may have been associated with the New York Heart Association class. We haven't reviewed how they dealt with that. That is just a point that the agency wanted to clarify.

DR. LASKEY: These issues did come up during the parent trial as well. We did pretty well rehash this and it is not new territory. I think the concerns are valid but we have been through this battleground.

DR. PACKER: Can I just ask Dr. Konstam a question? It is the imbalance that bothers you?

DR. KONSTAM: What imbalance?

DR. PACKER: The imbalance in the crossovers for worsening heart failure?

DR. KONSTAM: In the sense that I think it speaks to unblinding.

DR. PACKER: Yes. I am asking does the presence of an imbalance in crossovers for worsening heart failure lead you to believe that there was an unblinding?

DR. KONSTAM: That is one of the points, yes.

DR. PACKER: I just want to make note of the fact that in every heart failure trial ever done with an effective treatment for heart failure there are always fewer dropouts for worsening heart failure in the--

DR. KONSTAM: Yes, but it is ten to zero. For what it is worth, it is not 100 to zero but it is ten to zero. At the same time, we are seeing not enormous effects on things like quality of life scale and hospitalization differences.

DR. PACKER: I just want to make the point that any effective treatment for a disease is going

to reduce the number of patients who drop out for worsening of that disease. It has to.

DR. KONSTAM: Yes, but ten to one strikes me as excessive. We can go through the New York Heart Association class changes, for example, in the patients who were on treatment and I daresay we will find patients who worsened and, yet, didn't fall into this category of switching treatments because of worsening heart failure. So, I understand your point, Milton, but it just strikes me as excessive.

I just wanted to say something and see what your reactions are. The one disparity in the randomization, or differences between the two groups is in the frequency of ischemic heart disease. If I got it right, 63 percent of the patients in the on group had ischemic heart disease and 74 percent of the patients in the off group. This is somewhat concerning to me because I have the impression that patients who have non-ischemic heart disease tend to have a greater propensity to improve during the course of observation, either related to, you know, beta-blocker therapy that had been started a few months earlier or what-have-you. I think we see it in some clinical trials; I think

it is my own personal experience.

Again, looking at not enormous effects in subjective endpoints, I am a little worried that you have more non-ischemic heart disease in the on group. Maybe any of you can comment on that.

DR. PACKER: You know, imbalances occur. We wish we could prevent them. The only way I can address your point is that if you look only at the ischemic patients, and I am just looking at the subgroup analysis and these data have not been reviewed by the agency and this analysis has not been submitted for review, if you look only at the ischemic and, therefore, focusing on a patient population that would be balanced, obviously, for that, the delta between treatment and control for quality of life of life is 10. Remember, it was 9.5 for the overall trial. A difference in New York Heart Association class is minus one median, and it was true for the overall class. So, the point estimates for the ischemic only are superimposable over the point estimates in the overall trial.

DR. LASKEY: That is 90 percent of your data though, right?

DR. PACKER: What was that?

DR. LASKEY: What was the fraction?

DR. PACKER: I am just looking at this, I have to double the numbers, 124 non-ischemic, 248 ischemic.

DR. KONSTAM: I wanted to just ask, to make sure I have it, about the complications because I guess the complications are broken down into a lot of different categories and I am trying to sort of satisfy myself about the big picture and what is going on across all these events, and maybe you can help me. How shall I best do that, I guess is the question I have. I am looking at--

DR. YOUNG: Maybe we can ask you questions.

DR. KONSTAM: Oh, you can ask me anything you want. Your slide number 51, which is primary safety objective for InSync ICD related complications at six months, where observed six-month rate equals 81.1 percent. I guess that is freedom from event.

DR. LEON: Yes, that is correct.

DR. KONSTAM: Did these numbers include the coronary sinus dissections and perforations?

DR. LEON: Which slide are you referring to?

DR. KONSTAM: I am looking at your slide 51.

DR. LEON: These are complications attributable to the device itself. The coronary sinus-associated complications appear prior to that.

DR. KONSTAM: Events related to left ventricular lead, 54. It is your slide 51.

DR. WILKOFF: Slide 51 refers to post-implant. It is in follow-up.

DR. KONSTAM: So, when it says events related to left ventricular lead and there is a number next to it, 54, that does not include the coronary sinus dissections during implantation?

DR. WILKOFF: That is correct because these are post-implant.

DR. KONSTAM: I would like to get a sense of risk-benefit, and the only way I can do that is if I get something about overall risk, and that overall risk relates to implantation. I understand that placing the coronary sinus lead is technically much more difficult than regular pacing leads and there is a five percent, I think, event rate related to coronary sinus problems. So, it would seem to me that those numbers ought to be put

together with the more long-term adverse event rates in order to get sort of an overall view of the negatives to the patient in this. I don't know if we want to do that, or what, but that really is what I would be looking to. Can you do that?

DR. LEON: Yes. If we look at the total adverse events that were LV lead related in the study, adding complications and observations, it adds to 7.9 percent.

DR. KONSTAM: That includes these 54 then? It can't be; it must be more than that.

DR. LEON: No, these are specific to the LV lead.

DR. KONSTAM: But this says LV lead, 54; events related to LV lead, 54.

DR. LEON: Again, the intent was to present the complication rate associated specifically with the implantation procedure and then the lead events--

DR. KONSTAM: I got you, but if you add 54 to the implantation events it is more than 7 percent.

DR. WILKOFF: We don't have it put together right now, but I can give you a comparison group. Okay? So, we can give you the implant-

related problems with InSync versus the InSync ICD. I can't give you the combined number right now.

DR. KONSTAM: Well, if you can't, I think we should. I mean, I would like to see that. It seems like we could do that here based on the data you already have and get a real patient-related percent event rate related to the LV lead from the time you stick the groin to the time--whatever you stick.

DR. YOUNG: I am just curious because I think Dr. Konstam is pointing to something that concerns us all. We have a group of patients who are going to go for an ICD.

DR. KONSTAM: Right.

DR. YOUNG: What is the incremental problem that this more sophisticated lead placement brings in. Is that where you are going with this?

DR. KONSTAM: Yes, specifically with relation to this population, yes, and I think it has more global implication with regard to resynchronization therapy in general and the risk-benefit that is of interest.

DR. LASKEY: I am a little confused here; I shouldn't be, but is this the same lead that was approved for the parent? This is a different LV

lead?

DR. LEON: No, when you look at the implant-related complications, that covers an attempt to implant any of the leads listed. When you refer to the 4189 post-implant complications, those data refer specifically to that lead after implant, just as the 2188 and 2187 post-implant adverse events refer to the commercially approved leads after implant.

DR. KONSTAM: I would like to see a percentage related to LV lead problems overall, from beginning to end. I guess the last thing I would say, just to echo Mark's comments and Mike's comments, you know, I agree with Milton that generally speaking you are on shaky grounds when you start deciding on indications based on subgroup analyses, but, you know, I do believe, and I think probably most people believe, that there are subgroups of patients here that are potentially going to have a substantial benefit and there are numbers of patients here that are going to get no benefit.

The problem with doing a large study--I guess this is a medium size study, with endpoints like this is winding up with the impression that

everybody who meets entry criteria is fair game for this procedure, and I think that is a problem. That is a problem for us in the heart failure world. So, I think we need some work about this. I think we do need to look at the subgroups here.

I am also impressed with the inadequacy of QRS duration as being able to discern LV dysynchrony and the potential for benefit. I have seen some very compelling data in this regard, and you probably have as well. So, I think we are going to be looking for help about this. You do have echoes. Well, let me just ask a question, do you have any intent to explore baseline echocardiographic parameters of dysynchrony as a determinant of clinical outcome in this study?

DR. YOUNG: Sure. Even though we have just railed against sub-studies, we are going to be doing a heck of a lot of them. There is no question about that.

DR. KONSTAM: What about the echo analysis?

DR. ABRAHAM: Yes, we will do it. In fact, we believe we have now two very powerful databases between InSync and InSync ICD that can be analyzed alone or in aggregate to try to help

answer some of these questions. But I would just remind you that by analogy we don't really have good clinical predictors of responsiveness for virtually any therapy we use, and even the obvious ones don't often work out. For example, baseline heart rate and beta-blockade is a good example of an inconsistent finding that may or may not predict response. You know, we have looked, at least first cut, at the obvious things such as baseline QRS duration and change in some of these trials, and, like many other observations in other trials, you just can't find the predictor very easily.

DR. KONSTAM: Bill, I think your point is extremely well taken and I agree with it. I am more concerned about this because it is an interventional procedure as opposed to a medication that is relatively well tolerated. Also, here we have really good conceptual physiologic basis for looking at patients who might or might not respond and I think we ought to work at finding those.

DR. LASKEY: We have, for good reason, slowed down quite a bit. I would ask the group's indulgence. We are going to try and get through the voting panel's questions before the lunch break. People have to leave for flights and,

airports being what they are, we should try and honor that. So, let's try and get through this. Again, I would encourage people to focus their comments more on the lines of questions than editorials and so forth. Dr. Ossorio, please?

DR. OSSORIO: Thank you. I can be short, in part because I think most of my questions, if not all of them, have actually been touched upon already. I will just reinforce the thought that I am concerned about this 224 number and the censoring. I also had a question about if you have any data on inappropriate shocking. That was addressed.

My primary concern as an ethicist, of course, has to do with what I see as still a really problematic set of issues around whether the potential harms of this intervention outweigh the potential benefits of this intervention. So, the questions that Marvin was asking very much are trying to get there. I actually had a specific question about comparisons. You had mentioned that you have some comparisons. Maybe we could hear that.

DR. WILKOFF: If we try to tease out again those complications that are related to the

implantation of the additional lead--remember, all these patients are going to have an implantable defibrillator which comes with its own set of issues. But if we look at the left ventricular lead implantation-related issues, complications, and we compare the rate in the InSync ICD study to the clinically approved InSync trial, the overall rate was 7.9 percent in InSync ICD and 8.8 percent in the InSync study. So, very similar, slightly higher in the InSync study. This is data that you do not have, supporting data that we have. So, we looked at the InSync ICD LV lead-related implant complications versus the InSync, the pacemaker.

DR. OSSORIO: This was including problems also related to implantation itself or only post-implantation problems?

DR. WILKOFF: This is implant-related, left ventricular lead related, so not related to the right atrial, not related to the right ventricular, not related to the device itself, but the left ventricular lead only issues. In terms of intervention, that is the difference between this procedure and other procedures. It doesn't compare to not putting it in but this is the prevalence and it is not different than the clinically released

device that is out there today.

DR. BRINKER: Could you please clarify. I thought that there were 69 unsuccessful implants, which comes out to greater than ten percent failure of implant device. That is in defibrillator alone the failure to implant.

DR. WILKOFF: The number 69 includes the Class II patients. There were 50 in the Class III and IV.

DR. BRINKER: And that is over ten percent, and I don't care whether it is Class II, III or whatever. That is a large failure rate.

DR. WILKOFF: This is failure of the LV lead. That does not mean that the patients did not have an ICD implanted.

DR. BRINKER: That is a second question, but you just said that the failure rate was 7.- something.

DR. WILKOFF: No, I said adverse events where there was a coronary sinus issue or some sort of complication, not failure to implant. That is a different issue.

DR. BRINKER: All right--

DR. WILKOFF: There were 50 patients. Well, we can talk about the percentage of patients

that had successful left ventricular implants. Okay? So, the successful left ventricular implant rate was 93 percent, I think it was, in the InSync trial and 88 percent in the InSync ICD trial. When you compare those implant rates, which addresses your issue of how often you can actually get it in this way, those are not statistically different from one another, not distinguishable. The implant rate is very dependent upon the experience of the operators, and the average number of implants per center was much higher in the InSync than the InSync ICD. So, the answer is approximately 90 percent of the time you can actually get the lead there, and that is just part of this procedure.

In terms or complications, not implant success, in terms of complications the rates were about 8 percent in both groups.

DR. LASKEY: Can you keep us honest, is this per patient as unit of analysis or per mishap?

DR. WILKOFF: Let me make certain. This is per patient.

DR. OSSORIO: I just want to follow-up on this because you said approximately ten percent of the time you failed to get the lead where you needed it to be.

DR. WILKOFF: Yes.

DR. OSSORIO: And this additional percent of the time there is some further problem that happens later with that lead.

DR. WILKOFF: Well, they are overlapping and so it is not additive.

DR. OSSORIO: Okay. What I am trying to get a hold of is how many patients who got this device would have to have a second operation or would not get the benefit of the pacing, or whatever.

DR. WILKOFF: It is a complicated question, but it goes this way, all these patients had a defibrillator implantation. So, all of these patients would have gotten at least a right ventricular lead and a device. Then, another assessment would have to be made whether it was worth putting a surgically placed epicardial lead or to make another attempt when you are having a better day, whatever, you know, whether you thought you could do something different, and it is going to be individually determined. But all the patients, if they are indicated for a defibrillator, should be able to have their defibrillator implanted at that point of time to

get the defibrillator benefit and then it is going to be individually decided. Most of the time, what is decided is that you try for a period of time. You kind of figure out when you can't do it and you make a commitment up front. If this is an important thing to do, you will ordinarily recommend that an epicardial lead be placed at that point of time, but it is not universal; it is individualized and it just depends.

Let me make one other point. In both studies, the InSync and InSync ICD, when there were more than 20 implants in the center the implant rate was 95 percent. This is early in everybody's experience but with experience over 95 percent of the patients have the lead implanted.

DR. OSSORIO: So, that might suggest that if I am trying to think about what is the clinical significance of this, weighing perhaps a small benefit in terms of quality of life against--if I assume the very best case scenario, which is that people who end up doing this, if it is approved, are the ones who have a lot of experience, which perhaps is not a very good assumption, then I would be looking more at the failure rate post-implant of that lead.

DR. WILKOFF: Right.

DR. OSSORIO: Actually, I don't find this terribly helpful necessarily. Another question I have has to do, actually, with how few women were in the study. You said you had done that subgroup analysis and that there are no differences, and I know these are not data that have been presented.

DR. PACKER: These are not data that have been presented. There are only approximately 84 women so it is a small group of women, not all that unusual a percentage for heart failure studies. The magnitude of the effect on quality of life and New York Heart Association class is about comparable in men and women. We need to show all these to the agency and have them do the appropriate analyses, but the subgroups are small.

DR. OSSORIO: Yes, I guess I would just make one comment and then I am finished. The one comment is it is true that clinical trials overall have been pretty bad at recruiting people of color, very bad actually, and often not great at recruiting women. But just because we have been not great at it in the past doesn't make it okay. So, I am not really all that impressed.

DR. YOUNG: That is right on target, and

all of us doing clinical trials are so tuned into that fact and trying hard. I will say, interestingly enough, there were 25 percent women in this trial, which is a little bit higher than a lot of heart failure trials but we agree completely with you.

DR. PACKER: I just wanted to address the ethical issue here, it is a very important one, and at the same time address the magnitude of effect. I number of the members of the committee have characterized the magnitude of the effect here as modest, small, or whatever, and I don't want to put words in anyone's mouth but the best way, I think, to judge magnitude of the effect here is either to compare it with what we see with drugs or, alternatively, to compare it to the magnitude of what was seen in the InSync trial. Remember, what we are really asking here, and what the agency has requested of the sponsor--there is now an ICD device approved; there is now an InSync resynchronization device approved. So, the question isn't whether resynchronization works or whether ICD works. The question is whether patients who have both indications should be subject to two procedures. Whether patients who

have both indications should not only be subjected to two procedures, but subject to two devices that can interfere electrically with each other. That is a big concern.

So, the question really is, is the magnitude of the effect here similar to the magnitude of the effect seen in patients who have the same criteria but don't get an ICD, and the answer is yes across almost all variables. So, the value of this device is that it provides in one device a mechanism of satisfying both clinical indications as determined by a physician, whereas, in the absence of such a device there would be two surgical procedures and potentially the implantation of two devices that electrically interfere with each other.

So, the way that I think you need to judge risk to benefit here is to also compare it to the risk to benefit of putting in two separate devices, and the risk to benefit seen in this trial compared to the previous trial of resynchronization reviewed by the committee that led to the approval of the device.

DR. LASKEY: I respectfully ask that we move on. The question was more geared towards the

recruitment of minorities. We certainly appreciate the breadth of your response but I think we need to, again, limit the scope of the question and answer. Tony, please?

DR. SIMMONS: First of all, let me say that I think the sponsor did try to do a scientific study, which is commendable, and I think the FDA did a very nice job of trying to put the packet together.

But to address your last comment first, I am not sure that this packet addresses that issue. When I got this packet only a few days ago, when I first started reading this packet I thought that I was going to be trying to address the issue of synchronization that has been approved, ICDs that are approved, and is this device good enough to go on the market as a combination device, and I don't see that data in this packet.

Some of the things that Bruce was presenting was data that should have been presented a long time ago, are the issues that I wanted to see. How is this device programmed? How did is the AV interval programmed? What is the blanking period? Let's see some electrograms. There isn't an electrogram in this whole thing. That is what I

want to see, is this device electrically safe when the two things are put together, and that data is not here. That is sort of an editorial comment.

This goes to my other major comment since I know time is limited. I know Dr. Wilkoff to be scrupulously honest. He has been answering my questions for a long period of time so I am going to pick on him, and I hope you don't mind, Bruce. I am still trying to figure out what I would say to my patient that I was planning to put this device into because looking at this data, what I am saying is I look at the data and I see that there is a 10-15 percent failure rate right off the bat of getting these things in.

Secondly, I look at the 4189 lead and the numbers that I look at here are a lot higher than the numbers you are presenting. I mean, if you look on page six of the clinical review provided by the FDA, the model 4189 LV lead-related complications at six months--these are post-implant, there are 52 complications in 46 patients; 31 lead dislodgements with this. That is just the 4189 lead. And, that gives you a lower confidence interval of 80 percent at six months that that lead is not going to have a complications, not an

observation but a complication. Complications mean an intervention. That means a second surgery in most patients. In some of these patients, they are getting three surgeries because you have 52 complications in 46 patients.

Then you go back to your approved lead and you are still talking close to 90 percent lower confidence interval that this lead will not have a complication. So, in the best of all possible worlds, we are looking at I have to tell the patient there is some chance you are going to have a benefit but there is a 15 percent chance I won't be able to get the lead in, and there may be up to 20 percent chance you will have more than one surgical procedure before we can make this thing work. Is that true or not true?

DR. WILKOFF: As you know, Tony, this is not the easiest of all procedures and our experience is improving, and there is plenty of evidence for a training effect. As I said before, if you have done more than 20 of this and, indeed, if you did more than 20 in the InSync trial, the implant success rate of the left ventricular lead was over 95 percent.

So, what I would tell the patient in my

institution is that our failure to deliver the therapy is approximately five percent. And, as you know, the reason for failure to deliver the therapy is mostly related to what the patient gives me, whether there is a vein there. Now, what I tell the patients is that if it is technically feasible we will place this lead transvenously but I tell them up front that if I cannot deliver the lead or if it doesn't work properly we will strongly consider doing a fluoroscopic placement of the LV lead. So, I tell the patient that up front, and I think that that is reasonable. As a matter of fact, sometimes the technical considerations push you to put it in a suboptimal spot but you might still be better off putting it in epicardial.

After that, our experience in terms of dislodgements and everything like that also is that that is experience development. So, what you are looking at is an overlap of the technical development of the tools and the technical expertise over time. As we see it now, I have to say that there is a significant chance, and I tell every patient this, that we will not be able to place the lead. There is a significant chance that you might need a second procedure. On the other

hand, these are all patients that have been treated maximally with drugs and other therapies. They are not being offered anything else, and these patients want a chance. You know, there is a very significant chance that they can improve. I don't have another way of helping those patients that much. These patients want something more and I am up front with that. Quite frankly, there is no trouble convincing the patient to do this now, and there is no trouble before or after the InSync was approved. Patients are pounding on our doors to do this, and we are very honest with them and there are lead-related problems but it is getting better.

DR. SIMMONS: It seems like there is a significant training issue then. Have you got data on showing that there really is a decline in lead dislodgements with time with the number of implants? The other question is when did these leads dislodge? Did they all dislodge in the first 24 hours or did they dislodge throughout the entire six months of the study? And, how close a surveillance are you going to have of the patients to make sure the lead doesn't dislodge?

DR. WILKOFF: Let me address dislodgement. There are several aspects to dislodgement. One is

just dislodging out of the position in the RV or RA, but some of these dislodgements are just migration further out into the vein and now you are getting diaphragmatic stimulation, and such like that. Those kind of dislodgements you know about pretty quickly, sometimes when they get off the table, and such like that.

So, I think it is experience dependent. We are looking for the exact numbers in terms of the training effect. We have certainly got much better over time in terms of what is going on. But I also think that as the technology goes on it will be better.

There are physical characteristics of these leads. The 4189 lead is a very thin lead and it is particularly well adapted to going distally in a small vein. But some people have huge cardiac veins and the 2187 or the 2188 are better suited for those patients. In the clinical trials we steer people to one lead because we are trying to see the effect of that lead. I think people were pushed, for a very good reason, to put what I would consider the wrong lead, as experience has determined, into that particular sized vein because of the trial design, which was appropriate. But

now I would choose the larger lead to go into that particular vein. As we get more options, we are going to see for tortuosity, we are going to see for steerability, size, whatever else like that that the real answer as to how carefully we are going to have to look at this, in terms of detection with this particular device which is the most important thing, sensing is from the right ventricular lead. So, dislodgements are whether you are achieving biventricular pacing or not, but not as a safety concern in terms of ventricular tachycardia detection. I think I would be a lot more concerned in the defibrillator case if that dislodgement could mean over-detection of other arrhythmias, and such like that. Since we are assuring the life-saving portion of this particular product and the additional quality of life for BV pacing, I think it is not a safety issue. It is a clinical issue and we are going to have to look at it more closely as time goes on.

DR. SIMMONS: Well, did they all fall out in 24 hours?

DR. WILKOFF: No, it is a progression. Most of them happened early but not all of them.

DR. SIMMONS: So, are you going to

recommend some increases follow-up over a period of time to make sure the lead hasn't fallen out?

DR. WILKOFF: I think clinical follow-up for symptoms on a routine basis--do you have that?

DR. SIMMONS: While you are looking for that, tell me what happened when the RV and the LV lead were plugged into the wrong ports? How did you discover that, and what problem did that cause?

DR. WILKOFF: I guess there was one case where that occurred, and it is similar to the kind of problems you get when in an integrated bipolar lead you put the SVC and the RV opposite each other. What happens is that you start sensing from both chambers and you get double counting and you get combined sensing from the RV and the LV, which is like other biventricular devices. This is the only device that prevents that as long as you follow the labeling.

DR. SIMMONS: Well, how did you get the pectoral stimulation from the 4189 lead? What happened there? I don't understand. That was one of the complications listed, pectoral stimulation. Is that a fracture or is that some design problem that we should be worried about?

DR. WILKOFF: You know, I don't know. We

can take a look at that, Tony. It doesn't make a lot of sense to me.

DR. SIMMONS: Under complications of the ICD, ventricular tachycardia was listed as a complication also. What was that all about?

DR. WILKOFF: Is that during the implant?

DR. SIMMONS: No, post-implant, 11 events in 9 patients. Most of these complications were not really concerning, however, one was ventricular tachycardia and another one was electrical reset. What happened with the electrical reset?

DR. WILKOFF: There is a known rate of power-out reset that occurs with implantation devices. This particular device was explanted because we were uncertain of its reliability. We did the software reset on the device and there were no mechanical issues associated with that particular device. There are nine in the entire GEM series of defibrillators that occurred. This is one in this InSync. I think there are 75,000 GEMs and nine events in that particular category. I suppose it is possible that there is an intermittent component failure but the most likely thing is that it is a relationship to a stray gamma ray hitting a spot and flipping. Basically, the

most important thing to remember about this is if the device has any question about whether it is functioning properly, it resets itself. It is a safety feature. If there is any question whether it is functioning properly, it resets itself; puts itself in a safe mode. So, if there is any internal inconsistency, that is what it does. Then you can find out at the next point in time. But it still functions as a defibrillator during that period of time. It happens rarely. It is a known type of situation for implantation devices.

DR. LEON: Just to give you some data to answer some of your previous questions, we do not have data on implant center experience as it relates to lead dislodgement, but we do have it for primary success. As Dr. Wilkoff alluded to, for centers that have done between one and ten implants the success rate is 86 percent. As centers increased to 11-20 implants, the implant success rate increased to 92 percent. In centers that did more than 20 implants, the implant success rate increased to 95 percent. So, there is clearly a learning curve.

With respect with lead dislodgement, what we can tell you is that lead dislodgements have

been observed as early as one day and as late as 12 months after implantation and there is a fairly broad distribution, without really being able to pinpoint when it happens.

DR. WILKOFF: To answer your question about the VT episode, there was one patient that was hooked up correctly to the defibrillator, where there was a fractionated electrogram and the fractionated electrogram caused double counting and, therefore, that was the VT.

DR. LEON: With regard to the on patient's pectoral stimulation, the bottom line is the exact cause is not known. The lead was repositioned. In our experience in our center, not in this particular trial, we have had one case of pectoral implantation that was associated with unipolar pacing with a lead that was placed anterior to the chest wall and caused intercostal muscle stimulation.

DR. SIMMONS: I guess I have other questions but I know we need to move on.

DR. LASKEY: Yes, maybe if we just hit the high points.

DR. SIMMONS: Let me ask one other question and I will let it go then.

DR. LASKEY: Sure.

DR. SIMMONS: On the crossover patients, you know, as I kept reading about the crossover patients, it did make me feel that there is significant investigator bias. I mean, the investigator were clearly biased or there would have been some going in both directions. Somebody must have said this device is making the congestive heart failure worse; let's turn off the biventricular pacing. So, there is clearly bias going in that direction to turn the device on.

I am not a statistician so when you are analyzing with intent-to-treat and a patient gets crossed over from off to on, what happens to that patient and what happens to the data for that patient?

DR. PACKER: In an intent-to-treat analysis the patient who is crossed over from off to on at six months will be analyzed with the off group.

DR. SIMMONS: And his data will go into the off group?

DR. PACKER: Yes.

DR. SIMMONS: Well, see, that actually biases against the device--

DR. PACKER: Right.

DR. SIMMONS: That is what I thought. It bothered me that there is bias and it bothered me that the investigators were maybe not being completely up front but, at the same time, the result of the bias was actually to go against the study having a positive result. That is the way I interpreted that.

DR. PACKER: Can I just address the issue of the imbalance? I just want to reemphasize the fact that in any effective treatment--

DR. SIMMONS: How do you know it was effective? Who said it was effective? That is the thing.

DR. PACKER: If you look at every double-blind, placebo-controlled trial with any intervention, being it a drug or whatever, where blinding is not an issue there is always a greater number of dropouts for worsening of the disease in the group not getting active therapy. So, the question is not whether there should have been an imbalance. There should have been an imbalance. I think the key question which Marv raised earlier is why is it ten versus zero instead of eight versus six, if I can phrase it that way.

DR. SIMMONS: You know, if there was a clear benefit, I could maybe understand it. But when the benefit is so marginal and we are having a struggle here just to find out that there is a benefit, to say there is a clear benefit and that is why all those patients were crossing over--I don't know.

DR. PACKER: The magnitude of effect here is the magnitude of effect you see with interventions that work for the treatment of heart failure, and are similar to the magnitude of effect that led to the approval of InSync in absence of an ICD indication.

DR. LASKEY: We have been here.

DR. SIMMONS: Yes. Let me just say I would like to see at some point in time the sponsor get together a real number of data that would show how many patients failed to get their implant; how many patients failed with the lead being dislodged; and how many surgeries were reduplicated; and let's add them all up and get a real number that we could present to a patient and say these are your chances of having a successful implant without having multiple interventions and multiple complications. I don't see that I can dig that out of here right

now.

DR. LASKEY: Dr. Nissen?

DR. NISSEN: I will be uncharacteristically brief. First of all, let me say that I think this was a well-designed, well-executed and very well presented trial. Those of you who know me, know that I don't hand out such praise lightly. It is a very tough study and I particularly want to compliment the sponsor for having all the presentation come from the investigators and not from the company. That is very refreshing and it is rare, at least it is on the cardiorenal panel to see that, and I think it helps us a lot because we are talking to our colleagues about the study, not necessarily people who have a commercial interest in it.

I share many of the concerns raised by the panel about the fact that the p values were somewhat marginal on the primary efficacy parameters, and I share concerns about the blinding. Three things come up that tend to reassure me about the results. One is the magnitude of the effect. Tony, you know, if you tried to do a drug study of heart failure in this size patient population and you got a positive

result people would be very impressed because, in fact, given the magnitude of effect that you see with drug therapies you usually have to study thousands of patients to actually show a benefit on top of good therapy. Remember that these patients were actually treated well for their heart failure. So, the bar was set very high here by the fact that these patients were well treated and, in spite of that, there was an effect that, I agree, is not as large as we might have wanted but is very impressive in this setting.

The second thing that reinforces this is that whenever there is a marginal value on the primary efficacy parameter I look at the secondary endpoints. And, I am very impressed here that a whole slew of secondary endpoints are all going in the right direction, the exercise endpoints, the echocardiographic endpoints which are not easy to achieve. The point estimates are not always statistically significant but there is virtually nothing here, perhaps with the exception of norepinephrine, that goes in the wrong direction. To me, that is very reassuring and very reinforcing.

The third issue here is that we already

know from the previous InSync trial that in a larger cohort, pretty well studied, there was efficacy for this approach. So, the question I do find myself asking is the one you postulated, which is would it be better for patients to get one device or two? Because people are going to get this therapy. They are going to get defibrillators and they are going to get implantation biventricular pacemakers, and I think the sponsor did an excellent job of demonstrating that the overall benefit--and I think the ethical issues here are equally important, if I were a patient would I want to have two surgeries or one? The answer is I would greatly prefer one. Then, the only question is do you somehow screw up the efficacy of either therapy by putting them together, and I saw no compelling evidence that you do so.

My concerns are similar to other people's and I would say I have two concerns. One is that I am disappointed that there are not better predictors of who benefits because it means you have to use a blunt instrument on a broad range of patients in order to get some benefits. As I look at the directional changes on that scatter plot,

what I see is lots of people going in different directions, and I wish that there were some way to know whether somebody is going to be better or not with this therapy. You know with ACE inhibitors that pretty much everybody is going to do better. You don't know that, unfortunately, with this device. Milton can maybe comment on this, but I think that the dispersion of the results is more chaotic here than it is for a typical drug study where things tend to look a little bit more consistent. Maybe that is true and maybe that is not true. You can probably help me with that perhaps.

Then, the final question that I had would be about the issue of what happens to people in whom you can't place the lead or in whom the lead dislodges? I would like to have some flavor for what the outcome is in the treatment failure group. Do most of them end up undergoing another procedures with lead placement? Do they end up getting an epicardial lead? What actually happens to those people in whom there is a failure?

The two questions I guess I had are about this issue of the scattering or results, and any thought about that from the heart failure folks?

The other question is about the outcomes in the dislodgement, failure to place group.

DR. LEON: With respect to the outcomes in the group that had unsuccessful implants, what we can tell you is really the number of those patients that died, and we can tell you the acute complications associated with the implant. Beyond that, we have no data.

DR. WILKOFF: The dislodgements were resolved with another operation. Virtually all of the patients that were randomized, I mean, by design to get randomized you had to have a successful implant. So, all the people that were included in the trial had their leads resolved. Clinically the answer is that it is a non-zero event and that patients need to have additional procedures to have these placed. Clinically, what that means is that sometimes you need a surgical placement of that lead because the vein is just not available to do that implantation.

DR. NISSEN: Bruce, did any of the patients or their physicians elect to just bag it, to not even attempt to replace a dislodged lead? Does that happen?

DR. WILKOFF: It did happen. I think

there were four patients--this is worrisome but this is the way it goes--they said if I can't get a BV system I don't even want a defibrillator. So, they didn't allow us to leave the device behind. That was surely not at the encouragement of the physician, but the patient said if I am going to get the possibility of shocks for tachycardia, I want also the possibility of having BV pacing. So, sometimes they are going to decide not to do it.

DR. NISSEN: What about this issue of consistency of effect? Is it different from drugs?

DR. PACKER: You may or may not be reassured to know that chaos is characteristic of drug studies as well as device studies. In general, the degree of dispersion, or informally referred to as chaos, is pretty much directly proportional to the size of the trial. In trials that are very big, several thousand patients, when you do subgroup analyses the point estimates line up pretty well. There are some exceptions to the rule but you usually get that consistency when you study large numbers of patients. If you study, you know, 300 or 400 patients, presumably because of the effect that outliers have on small subgroups, you get a more chaotic pattern. So, my sense is

that what we are seeing here is actually rather characteristic of any evaluation, be it drug or device, where the N is what the N is here as opposed to an N of 2000 or 3000.

DR. NISSEN: One final comment before I yield the mike, and that is that I was interested to see that although it didn't make statistical significance there were less VT/VF episodes in the group that had the pacer on. I took note of that and I asked myself the question in a larger sample, followed for longer, does improving the heart failure with biventricular pacing lead to less potentially lethal dysrhythmias, and I would encourage the sponsor to pursue that because that would be further reinforcing for me that if somebody has to refer patients to you, guys, to get this thing done, it is a good thing to do.

DR. YOUNG: I noted that, and I have to admit that in bringing the heart failure team into the EP world one of the things we were saying was, gee, maybe there are some things that look like a drug effect that we are doing. If we change some of these basic physiologic parameters, might that not be an antiarrhythmic treatment that is totally separate from the VT protection.

DR. LEON: And I believe there are results from another clinical trial of a resynchronization device that are consistent with this, showing a decreased incidence of arrhythmic events in the patients actively treated.

DR. NISSEN: It might be nice to do a meta-analysis on some of these trials, put them altogether and find out if this is, in fact, a reproducible effect.

DR. LASKEY: Thank you. Again, what I am shooting for is to wrap this up by 1:00 so that we are done and we can break for lunch. Dr. Aziz?

DR. AZIZ: I am going to sort of just target my questions to surgical sort of scenarios. I think 13 patients had dissections and perforations. How many of them actually had an open procedure? Were you able to just use cardiocentesis in cases that needed it?

DR. LEON: No patient had an open procedure. The most invasive procedure was percutaneous pericardialcentesis.

DR. AZIZ: In patients in whom you couldn't obtain the vein, did you use ultrasound to sort of guide you to find a vein?

DR. LEON: We have not done that at our

center. It was not systematically done. There are reports of that, and it does not appear to be incrementally helpful. I will ask Dr. Wilkoff to talk about his experience but we don't have specific data from this study to answer your question.

DR. WILKOFF: The number one indicator of how good you are at getting into the coronary sinus is practice. It just takes time. These hearts are dilated and distorted, and after a while you learn how to find the spots. But some of them you don't find because they are too small to get into. Some people even have absent coronary sinuses. What we have done in a few patients is spiral CTs to try to identify the location in the atrium and also the diameter. In some situations we have decided not to go ahead because there was just nothing to see. But those are difficult analyses actually.

DR. AZIZ: I am sure in the future there will be patients who will have, let's say, prosthetic tricuspid valves. Could you envision this system being implanted in those patients? I am sure they are more difficult.

DR. WILKOFF: You know, the interesting thing is one of the best side benefits of the

developing of the left ventricular lead technology is that we don't have to go across the tricuspid valve to pace some patients. So, people who have atretic or problematic tricuspid valves, now I have the tools to put leads to pace the ventricle and we don't have to go across the tricuspid valve. Inherent in this particular device though is that I need a defibrillator lead, and if I were going to be really aggressive about this what I would do is put a defibrillator lead down the middle cardiac vein, which goes posterior and proximates where the right ventricular lead goes, and then put another lead out to the coronary sinus. But that is being creative. But this gives us the opportunity. Those are the kind of clinical situations, having these kinds of tools, that we can start to do. Without this kind of a tool we can't approach those kind of patients at all.

DR. AZIZ: Either in this study or the InSync study, in patients who happened to die from any other causes were you able to look at the coronary sinus? Was there thrombus there, or was the lead well implanted? Do you have any data on that?

DR. LEON: I don't believe we have any

necropsy data at all from either of the two studies that would be meaningful.

DR. AZIZ: You mentioned that there were a number of patients who had mitral regurge. Clearly, by using biventricular pacing you have obviously shown that they feel better. But from what I can see on the table, the mitral regurge didn't improve.

DR. LEON: Not in the InSync ICD, mitral regurge did not decrease.

DR. AZIZ: And the EF didn't change?

DR. LEON: The EF went up by three percentage points, p 0.06.

DR. KRUCOFF: I am going to have the opportunity, if nothing else, to respectfully disagree with some of my dear friend and colleague, Dr. Nissen's overall comments. I am actually mad at you guys, and it is not just you guys. But I remember at the end of the InSync presentation paying you the compliment that was due at that time for a really tight presentation of a well-designed study where the results and the clinical relevance of those results to patients was readily evident.

I have had a headache with this pack since I got it. I really don't feel, like, for the

enormous experience and concern and dedication to this patient population that you guys have that I am in a good position to say much of anything about whether this device ought to come to market.

The question of the denominator, that is not complicated. It shouldn't even be a question. That should have been clear. It should be clear to us. We shouldn't have had to spend so much time on it, and I can say that on both sides of the review. When I read through this, both the fundamental material and the FDA review, I really walked away thinking I am looking at 80 percent of the relevant data; I am looking at an incomplete data set and what the heck am I going to do with that? Now what I am hearing is maybe that is not the case, and I think that that is a disservice to everybody, particularly the patients who might benefit from this if it works.

I can certainly say that I totally agree that for quality of life data this is a huge finding. I think for those of us familiar with how these things translate into patient care and the clinical relevance, Janet, I can say in a heart beat I think the level of this difference being clinically meaningful is without question. It is

just how you weigh that in, and this is where I am getting mad again, is what we clearly need to know is not fractured pieces of where the risks of this procedure are but overall where the risks of this procedure are. I think that has been detailed and I think several people have asked those questions, but this should have been put together up front.

The Hochberg is basically an interesting, complex and important way of looking at multiple co-primary efficacy endpoints. To then take fractured pieces of safety information and sit down and try to calculate what is the risk that we weigh against this benefit, particularly when you could see this coming, that the Hochberg really qualified very differently this time than in the InSync study, instead of all three variables being overwhelmingly positive, you could see it coming that you have one that is overwhelmingly positive at a very high level, quality of life; one that is on the edge, depending on how you determine who is in the denominator; and one, the six-minute walk, that just doesn't budge, to then have such difficulty in trying to figure out what we want to know in this patient population. This is a patient population who weren't defibrillator implantations,

in whom we are talking about superimposing another technology because they also have heart failure.

I disagree with Steve. I do not think the comparison here is that this one device versus two. There is no known information to suggest that biventricular synchronous pacing works in this patient population. In fact, the other trial that we reviewed when your first study came through looked at this patient population and the data did not suggest that it was effective enough to warrant approval of that device. Now there are different issues, but I don't think it is fair to say that the issue here is whether to put in one device or two. This is a vulnerable patient population who warrant defibrillators, and if we are going to superimpose additional technology we deserve an honest look at what does that mean to the patients and what do we tell them.

So, we need an overall LV lead risk measure to balance this against. How much added time is involved; how many times do you fail to be able to put the darned thing in altogether; how many times do you put it in and think you have got it in and actually it fails at a later date; how many times do you try to put it in and actually do

harm, dissect the artery, perforate, whatever. That cumulatively is the added risk of this procedure technically.

Then what I also feel like we are totally missing is what about the programming? Are we talking about taking functional ICD platforms that we know work and save lives and programming them around this thing so it won't interact or cross-talk? Or, are we talking about leaving the ICD platform in place and programming biventricular synchronous pacing around that? I can't tell. Maybe somebody can give me an answer to that, but from this panel pack I can't tell.

In fact, some of the things that Helen put up on the board in terms of how more than a majority of these were actually programmed worry me. It looks to me like the ICD is being programmed around the biventricular synchronous pacing, and if that is wrong I apologize. I just really can't tell, but I am concerned because I don't even know--maybe I will just stop and quickly ask just a dumb question, when the defibrillator goes into an event and starts following algorithms to deal with, say, a tachyrhythmia what happens to the LV lead? Does it stop pacing? Does the

biventricular mode continue? What happens?

DR. WILKOFF: Any pacemaker, and that is the biventricular part, when it senses a ventricular inhibits pacing. So, if there is any fast rhythm biventricular pacing is automatically eliminated. Okay? So, there is no overlap in that situation.

DR. KRUCOFF: So, if you defibrillate and there is no intrinsic rhythm and you start to pace, it is just the RV lead?

DR. WILKOFF: No, no, once it is terminated in that one beat it is already biventricular pacing again. It is on a beat to beat basis. Every ventricular event that is fast inhibits biventricular pacing, and every time there is a slow enough rhythm, every time it paces, it will biventricularly pace.

DR. KRUCOFF: I am not sure I am either hearing or getting the answer. If you defibrillate and the patient's intrinsic rhythm is asystole, the pacemaker function that is the next step in the algorithm is biventricular?

DR. WILKOFF: Yes.

DR. LEON: Suspension of pacing therapy is temporary and it reverts to the biventricular

pacing mode upon the recognition of asystole.

DR. KRUCOFF: Okay. May I ask another dumb plumber question? How do you know when you have LV capture? Is it by looking at the duration of the QRS complex? How do you know?

DR. WILKOFF: Well, there are a number of different ways. With this particular device we have very good ways of testing, different than with other devices. We can program to the LV only mode and look at capture and we can go the RV only mode and we can determine capture as individuals. We can determine capture thresholds and then do a threshold margin in order to assure consistent capture. We have a slide that shows two things.

A very good question is to suggest that, first of all, are we pacing the heart frequently? If we are pacing, then are we capturing the heart? So, are we delivering the therapy? Those are the two questions that have to be answered. The answer to the question is that since we are comparing this we should not be pacing the heart in those patients where the therapy is off, and we should be pacing the patients where the therapy is on.

[Slide]

Over here, this is the percentage pacing.

So, the device actually counts off and it paces. It gives you percentage pacing. These are the people who are getting cardiac resynchronization therapy. So, this is the number of people that are getting paced beats instead of sensed beats. These are the patients that are the control patients. You can see that the control patients were not getting paced, and the CRT patients were consistently having pacemaker output, biventricular pacemaker output.

Now, at follow-up we also looked at whether we had captured threshold and keep a margin above that to make sure that we have it consistent. So, we can have a capture margin of over 100 percent in over 85 percent, and more than 50 percent in most of the rest of the patients. So, although I can't tell you, you get 100 percent pacing and 100 percent biventricular capture in all cases, it was very largely delivered to this population. Over 85 percent of the patients had clearly efficient enough leads to show that we had consistent delivery of the therapy.

DR. LEON: In keeping with the request earlier, the data on the right half have not been submitted to the FDA.

DR. KRUCOFF: Thank you, that is very helpful. Really the last thing that I guess I wanted to touch on was that we have talked a lot about the blinding issues and in this kind of study it really is hard. Yet, having come down to a quality of life assessment, Bill, I think you made the point this is a patient-driven marker and my question or my concern actually is not about the physician blinding but about patient blinding. I am just going to ask you, are you really convinced that for all the ECGs and clinic visits you had no patients who knew what therapy they were getting, other than the ones who were deliberately cross over?

DR. ABRAHAM: I think it is difficult and dangerous to say no with 100 percent certainty, but I think with a very high degree of confidence patients maintained their blindedness in this study. I mean, there were three instances in which patients were reported to be unblinded. I know your concern is whether or not this represents a tip of the iceberg phenomenon. I don't think so. I think, if anything, we tended to over-report rather than under-report on blinding.

Let me just give you one example. We had

a log that listed the blinded and unblinded participants in the study. For example, if my study coordinator was listed as a blinded participant and was on vacation and another coordinator, not listed in that log, covered for her and did an assessment, that would be reported as an unblinded participant in the study when, in fact, that person was still blinded, not technically in the blinding log but for all intents and purposes in the study. So, I think the spirit and, in fact, the implementation of blinding was very good for both the clinical assessment as well as the patient assessment, and I think there is less question about the patient in this instance.

DR. KRUCOFF: Another plumber question just to help me, Bill, when you look at a surface ECG of somebody who has biventricular synchronous pacing on, can you tell from the surface ECG? Are there double spikes?

DR. LEON: Can I answer that question because this has actually been an interesting point for us? One thing we have learned is that we have had to emphasize the correct interpretation of electrocardiograms. The habit in a lot of EP labs and a lot of implant labs in follow-up has been to

look at one lead of the electrocardiogram because the rest of it is irrelevant. I will tell you that if you analyze the 12-lead ECG, particularly with attention to the initial forces of depolarization, it is very easy to tell if someone is biventricular paced and specifically when the left ventricular lead is capturing or not capturing.

DR. KRUCOFF: I guess my concern is how many of these folks on an ER visit or a clinic visit or their internist visit--I guess we don't have too many OB-GYN visits, but how many of these visits--

DR. LEON: I don't think most of the people you describe would be able to detect it on the basis of what I just explained.

DR. KRUCOFF: My question is how many of these folks would say what the hell is that?

DR. ABRAHAM: We did have a mechanism to try to maintain the blind in that setting as well, and that is patients carried a card that identified them as participants in a blinded study and implored the ER physician, primary care physician, whoever, not to unblind the patient. Obviously, there is some faith that patients presented that card at the appropriate time and that that was

followed but, again, that was an additional layer that was included in this study to try to prevent inadvertent or accidental unblinding in that setting.

DR. KRUCOFF: Again, I applaud the integrity and the effort expended. It is difficult, living on a quality of life measure for the whole efficacy case, even at a very large level of improvement in quality of life, to weigh added risk to your defibrillator platform and/or to the surgical procedures necessary to sustain this technology. That is where I am going to have a dilemma on where to go next.

DR. ABRAHAM: If I could just respond to that because this is where you started with the conversation as well. I just want to highlight the patient population that was studied and the patient population for which the therapy is intended in this packet. These are patients with Class III or Class IV heart failure despite optimal standard medical therapy. There really are few other treatment options for these patients.

When you think about risk/benefit--and I appreciate your criticisms. Perhaps we could have presented the aggregated data on incremental risk

associated with the LV-lead placement in a more cogent fashion, but that is really what we are benefitting, or what we are analyzing is a benefit in this needy group of patients.

These are not asymptomatic patients or mildly symptomatic patients but patients who remain markedly symptomatic despite adequate therapy to the incremental risk added by the additional lead.

DR. KRUCOFF: I take the point that desperate situations may warrant desperate measures but, before that point, I think we have "Do no harm." I think that how we put these data together ultimately needs to leave us with an ability to assess that.

DR. LASKEY: Dr. Brinker?

DR. BRINKER: A couple of questions because most of my concerns have been addressed. One is just for Mitch, that any pacing--you wouldn't have to know whether they are biventricular pacing. Any pacing on an electrocardiogram would show which group the patient was in.

DR. LEON: We misunderstood the question. Your point is very well taken. Someone who looks at an electrocardiogram should be able to tell

fairly quickly that the patient is either active therapy or not active therapy because of the delivery of the pacing spike tracing the p-wave.

DR. BRINKER: Let me just ask--the overall concern I think most of us have expressed concerns the risk/benefit ratio. I am not so concerned about a detailed analysis of the left-ventricular lead because I can get that intuitively if you just give me the numbers. I want to know, as the patient shows up for this study, and he goes in to get an implant, at the end of six months, what is that patient's chance of remaining in a biventricular mode.

That is number one. Number two, how many other procedures were required to keep in that mode. So, the up-front question is when they presented, you had about a 10 percent failure rate. None of those patients had a repeat procedure. Once they had a failure rate, this 10 percent, 69 patients, or 50 depending on how you look at it--none of those patients could were taken back and reappear here in another format. Is that correct?

DR. WILKOFF: No; it is not correct. If we look at all the patients, and this is functional Class II, III and IV, there were a total of 636